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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/367,714	01/14/2000	YECHIEL SHAI	SHAI=2	4669

1444 7590 03/18/2004

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/367,714	SHAI ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-14,20,21,27-29,35 and 37-39* is/are pending in the application.

4a) Of the above claim(s) *2-5 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,8-13,20,21,27-29,35 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the amendment filed 1/12/04, claims 1, 2, 6, 8, 12, 14, 20, 27-29, 35, 37 have been amended, claims 7 and 30-34 cancelled, and claims 38-39 added. Claims 1-6, 8-14, 20, 21, 27-29, 35, 37-39 are now pending. Claims 2-5 and 14 are withdrawn from consideration since they do not encompass the elected specie. Claims 1, 6, 8-13, 20, 21, 27-29, 35, 37-39 are examined in this Office action.

Applicants' arguments filed 1/12/04 have been considered and found not persuasive.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-29 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 27 recites that the composition (of claim 38) will be effective to treat infections caused by pathogenic organisms. Such pathogenic organisms include bacteria and fungi.

Claim 29 recites that the composition (of claim 38) will be effective to treat cancer. However, claims which recite treatment of infectious disease or treatment of cancer lack enablement. The specification provides data which shows that several of the claimed

peptides can inhibit bacterial growth *in vitro*. The specification also provides data which shows (pp. 51+) that peptides 1 and 16 are effective against *Candida albicans* and *cryptococcus neoformans* in vitro. The specification shows (pp. 52+) that peptides 23 and 24 inhibit proliferation of mouse adenocarcinoma cells. Also presented (p. 53) is data indicating inhibition of *leishmania mexicana* in vitro. In addition, on page 53-54 it is stated that peptide 23 will inhibit viral-induced hemolysis *in vitro*. It is stipulated at this point that each of these inhibitory processes will occur *in vivo* as well. But that does not mean that any of the peptides will be effective therapeutically. For example, if bacteria are reproducing at a rate of 100 "units" per day (in a mammal) in the absence of the peptides, and 90 units per day in their presence, one could say that inhibition had been achieved. But it does not necessarily follow therefrom that the patient's condition will improve. If the bacteria are still reproducing at a rate of 90 units per day, their population will continue to increase, in spite of the inhibitory peptide that is present; the patient's condition will only worsen.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

The following references teach "failure" in the treatment of ulcers that are caused by *Helicobacter*; as such, they contribute to the assertion of "unpredictability" that is made by the examiner:

Phillips, (*Helicobacter* 6, 151, 2001);

Pilotto (*Digestive and Liver Disease* 32 (8) 667-72, 2000);

Leung (*Expert Opin Pharmacother* 1 (3) 507-14, 2000).

In addition, Otvos "Insect peptides with improved protease-resistance protect mice against bacterial infection" (Protein Science **9** (4) 742-9, 2000) discloses one peptide that is active *in vitro* but not *in vivo* (due to the rapid decomposition in mammalian sera). Again, *in vitro* data are not necessarily predictive of *in vivo* efficacy. In addition, there is the problem of antibiotic resistance. The following two articles discuss this matter:

Liu (*Advances in Experimental Medicine and Biology* 455, 387 1999)

Monroe (*Current Opinion in Microbiology* 3(5) 496-501, 2000).

In accordance with the foregoing, in vitro antibacterial activity is not "predictive" of therapeutic efficacy.

The following references discuss the matter of various attempts by oncologists to treat cancer: Viallet (*Lung Cancer* **15** (3) 367-73, 1996); Kemeny (*Seminars in Oncology* **21** (4 Suppl 7) 67-75, 1994); Newton (*Expert Opinion on Investigational Drugs* **9** (12) 2815-29, 2000); Giese (*Journal of Cancer Research and Clinical Oncology* **127** (4) 217-25, 2001);

Garattini (*European Journal of Cancer* **37** Suppl 8 S128-47, 2001); Ragnhammar (*Acta Oncologica* **40** (2-3) 282-308, 2001). As is evident, attempts to treat cancer using agents which have exhibited *in vitro* activity leads to "unpredictable" results. Given the absence of guidance presented, the absence of working examples showing therapeutic efficacy, the state of the prior art, and the unpredictability of the art, the skilled artisan would conclude that "undue experimentation" would be required to practice the claimed invention.

*

Claims 8-13, 37, 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Each of the cited claims is drawn to a genus which encompasses peptides in which all of the amino acids are of the D-configuration, and which peptides, at the same time, do not require the presence of an "alpha-helix breaker moiety".

In the application as filed, all of the peptides described had to meet one of the following conditions: (a) both D- and L-amino acids were present, (b) all of the amino acids could be of the "D" configuration as long as an "*alpha*-helix breaker moiety" were present, or (c) if the peptide were characterized as a random copolymer meeting certain requirements, the language could possibly be interpreted as including the possibility of a peptide consisting entirely of D-amino acids. Each of the cited claims clearly encompass peptides that consist entirely of

D-amino acids, without, at the same time, requiring the presence of an alpha-helix breaker moiety. It does not appear that there is descriptive support for such a genus.

*

Claims 1, 6, 8-13, 20, 21, 27-29, 35, 37-39 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites (lines 6-10) that the meaning of the term "non-hemolytic" is such as to include cytolysis of red blood cells at concentrations higher than what is required to induce cytolysis of pathogenic cells. At the same time, lines 25-26 of claim 1 recite that cytolysis of red blood cells by the peptide is precluded. Thus, at one point, the claim recites that peptides which induce cytolysis of red blood cells are included, and at a later point, the claim recites that peptides which induce cytolysis of red blood cells are excluded. Accordingly, the claim is unclear as to which limitation controls. The same issue is present in each of claims 8 , 12 and 39.

Claim 21 recites a ratio, but it is unclear what the ratio is referring to. Ambiguity arises because the stereochemistry of lysine is unspecified, and similarly the stereochemistry of the first recitation of leucine is unspecified.

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 8-11 are rejected under 35 U.S.C §102(a) as anticipated by Shai (*J. Biol. Chem.* **271**, 7305, 1996).

As indicated previously, Shai teaches (table I, p. 7306) several peptides that are antibacterial but non-hemolytic, and which otherwise meet the requirements of the claims. In the previous Office action, several claims were rejected under §103 as obvious over Shai (rather than anticipated). Each of claims 8-11 is now anticipated by Shai because the previous exclusion of SEQ ID NOS: 1, 12 and 14 has been eliminated from these claims. The argument advanced (response filed 1/12/04) is that if one were to take each of the D-amino acids in the Shai peptide sequences, and replace them with L-amino acids, the result would be peptides that are found in nature. However, this assertion appears to be unfounded. The peptides of Shai require the presence of the following amino acid, wherein "X" is ethylenediamine:

$$H_2N\text{-}CH(CH_2\text{-}CH_2\text{-}COX)COX$$

There is no evidence that this amino acid occurs in nature to begin with, and certainly there is no evidence that this amino acid occurs as part of one of the peptide sequences given in Shai (even apart from the issue of "D" versus "L" amino acids). The argument on pages 16-17 of the response (filed 1/12/04) is actually somewhat contradictory. On the one hand, the response states that the claims do not encompass peptides which are obtained by modifying an amino acid of a naturally occurring peptide (setting aside the issue of "D" versus "L" amino acids). On the other hand, the claims do encompass peptides in which the amino acid sequence is not found in nature. Thus, if one takes a peptide that is found in nature, and modifies one of the amino acids such that the amino acid (which has been modified) does not occur in nature, the result has to be an "amino acid sequence" that is not found in nature.

Accordingly, the second, third and fourth peptides listed in table I of Shai would not be found in nature even if all of the D-amino acids were replaced with the corresponding L-amino acids. The claims are anticipated.

*

Claims 1, 8-12, 20, 21, 27-29, 38 are rejected under 35 U.S.C §102(e) as anticipated by Maloy (U.S.P. 5,792,831).

Maloy teaches cytolytic peptides containing D-amino acids. Also disclosed (e.g., col 4, line 43, col 5, line 30+, col 27, line 59) is that the peptides are not hemolytic. Maloy also discloses (col 27, line 10+) the following peptide, in which each of the amino acids is

of the "D" configuration:

LLKKLKKLLKKLLKLL

Claims 1 and 20 are anticipated because the peptide at col 27, line 10+ consists of a hydrophobic, a positively charged, and a D-amino acid. The leucine fulfills the roles of both hydrophobic and "D" amino acid, and the lysine fulfills the roles of both "positively charged" and "D" amino acid.

Maloy also discloses SEQ ID NO: 9 in which each of the amino acids is of the "D" configuration. This peptide is the following:

L-L-K-K-L-K-K-L-L-K-K-L

Claim 20 is anticipated because the amino acids D-lysine, D-leucine and D-Leucine are present in a 2:1:1 ratio. That is, the first recitation of leucine in claim 21 can be interpreted to include the D-isomer. Claim 12 is also anticipated, since this is a 12-mer in which at least 1/3 of the amino acids are of the D-configuration. Claim 12 requires that this peptide be a diastereomer. However, nearly all peptides are "diastereomers". Any peptide which contains at least two (chiral) amino acids other than glycine will be a diasteriomer of another peptide. Consider again the peptide disclosed by Maloy ("X" represents D-lysine):

L-L-K-K-L-X-K-L-L-K-K-L

This is a diastereomer of the corresponding peptide in which "X" is L-lysine.

In addition, Maloy discloses various peptides such as SEQ ID NOS: 1-11 in which all of

the amino acids are of the D-configuration. Claims 8-13, 37, 39 permit all of the amino acids of the peptide to be of the D-configuration. Claim 1 permits all of the chiral amino acids to be of the D-configuration, as long as an *alpha*-helix breaker moiety is present. As indicated on page 5, line 29+ of the instant specification, an *alpha*-helix breaker moiety would include simply the amino acid glycine. Many of the peptides disclosed by Maloy contain an *alpha*-helix breaker moiety, and as such, meet the requirements of claim 1.

✧

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1 and 27-29, 38, 39 are rejected under 35 U.S.C. §103 as being unpatentable over

Shai (*J. Biol. Chem.* **271**, 7305, 1996).

As indicated previously, Shai teaches (table I, p. 7306) several peptides that are antibacterial but non-hemolytic, and which otherwise meet the requirements of the claims. The argument advanced (response filed 1/12/04) is that if one were to take each of the D-amino acids in the Shai peptide sequences, and replace them with L-amino acids, the result would be peptides that are found in nature. However, as indicated above, this assertion appears to be unfounded. The peptides of Shai require the presence of the following amino acid, wherein "X" is ethylenediamine:

$$H_2N\text{-}CH(CH_2\text{-}CH_2\text{-}COX)COX$$

This amino acid does not occur in nature to begin with, nor do the peptides disclosed in the reference which contain this amino acid. Claim 1 encompasses SEQ ID NOS; 1, 12 and 14, and since Shai discloses peptides which are identical to SEQ ID NOS; 1, 12 and 14, it is appropriate to reject claim 1 over Shai for this reason. This ground of rejection is in addition to the §102 rejection above; this rejection is directed to close structural homologs of SEQ ID NOS; 1, 12 and 14. As indicated in the previous Office action, a peptide biochemist of ordinary skill would have expected that if the side chain of a single amino acid were extended or reduced by one methylene unit, the result would be a peptide with substantially the same activity as was observed before the modification [*In re Shetty* (**195** USPQ 753) and *In re Hass & Susie* (**60** USPQ 544)]. Setting aside the issue of "D" versus "L" configuration, the peptide disclosed in Shai is the following, wherein "X" is

phenylalanine:

GFXALIPKIISSPLFKTLLSAVGSALSSSGGQE$(NH_2)_2$

A peptide biochemist of ordinary skill would expect substantially the same antibacterial activity for the peptide in which "X" is phenylalanine as would be observed for the otherwise identical peptide in which "X" is phenethylglycine. The response filed 1/12/04 argues simply that (a) the Shai peptides occur in nature, (b) since they occur in nature they are excluded anyway. However, as indicated above, this argument is not persuasive because one of the amino acids in the Shai peptides is not naturally occurring. However, even if applicants could show, at some point in the future, that the Shai peptides do occur in nature, this ground of rejection would be maintained.

Thus, the claims are rendered obvious.

✧

Claim 39 is rejected under 35 U.S.C. §103 as being unpatentable over Maloy (U.S.P. 5,792,831).

The teachings of Maloy are indicated above. Maloy does not disclose a mixture of two or more peptides. However, it would have been obvious to one of ordinary skill to combine two peptides for additive effects, whether the goal of inhibition of bacterial growth or inhibition of tumor growth.

Thus, the claim is rendered obvious.

✧

Claims 1, 8-11, 27-29 are rejected under 35 U.S.C. §103 as being unpatentable over Paradies (USP 4,874,850).

Paradies discloses (col 47, line 59) that the tuftsin peptides of the invention are not hemolytic. Paradies also discloses that tuftsin is antineoplastic.

In col 69, line 63 the following tuftsin peptide is disclosed:

Thr-Lys-D-Pro-Arg

It may be the case that the tetrapeptide T-K-P-R is naturally occurring, and that therefore the peptide T-K-P-R *per se* is excluded from the claims. But this ground of rejection is based on the assertion that each of the following peptides would have been obvious to the peptide chemist of ordinary skill ("Orn" = ornithine; "Apg" = amino-pentylglycine):

Thr-Orn-D-Pro-Arg

Thr-Apg-D-Pro-Arg

The peptide biochemist of ordinary skill would have expected, a priori, that a peptide containing lysine would exhibit substantially the same activity as an otherwise identical peptide containing aminopentylglycine or ornithine.

Thus, the claims are rendered obvious.

✧

Claims 1, 8-11, 27-29, 38 are rejected under 35 U.S.C. §103 as being unpatentable over

Paradies (USP 4,874,850).

Paradies discloses (col 46, line 34+) that gramicidin S is an antibiotic. Also disclosed (col 47, line 58) that cyclic gramicidin S is not hemolytic. On the page containing columns 67-68 (USP '850), the structure of gramicidin S is provided; it is a cyclic peptide that contains two D-amino acids, and has a charge greater than +1. Paradies does not characterize gramicidin as cytolytic. However, one of ordinary skill would expect that if a compound is cytotoxic to microorganisms, it is cytolytic. Furthermore, this is the implied assertion in the specification. The specification provides data (pages 49-53) which show that the claimed peptides inhibit growth of pathogenic cells. The specification then implies that merely because the peptides inhibit growth of pathogenic cells, they must be cytolytic. Accordingly, by the criteria embraced by the specification, the peptide of Paradies is cytolytic. The claims also require that, in effect, if each D-amino acid is replaced with the corresponding L-amino acid, the resulting peptide must not be found in nature. There is no evidence that if the D-amino acids of Gramicidin S (disclosed in Paradies) were replaced with the corresponding L-amino acids, the result would be a peptide that is found in nature.

Accordingly, the disclosed gramicidin compound meets the limitations of the claims, and the claims are rendered obvious.

✧

Claims 1, 8-11, 27-29, 38, 39 are rejected under 35 U.S.C. §103 as being unpatentable

over Jacob (USP 5,635,479).

Jacob discloses peptides that can be used to inhibit growth of cancer cells, and to treat cancer patients. Among the disclosed peptides are SEQ ID NO: 115 and SEQ ID NO: 117 in which all of the chiral amino acids are of the D-configuration, but which peptides also contain glycine. Also disclosed col 22, line 5+ and table I (col 21, line 18+) is that the two peptides (in which all of the chiral amino acids are of the D-configuration) extended life of rats which had been injected with ovarian teratoma cells (see also figures 1-4). The reference does not explicitly state that the peptides are more effective at killing cancer cells than they are at inducing hemolysis.

The first point is that the claims do not exclude peptides in which there are no L-amino acids, and at the same time, all of the chiral amino acids are of the D-configuration. As indicated on page 5, line 29+ of the specification, an *alpha*-helix breaker moiety would include simply the amino acid glycine. Both SEQ ID NO: 115 and SEQ ID NO: 117 meet the limitation of containing an *alpha*-helix breaker moiety.

The second point concerns hemolysis. The instant claims encompass the possibility that the peptide exhibits no hemolysis at all. But the claims also encompass the possibility that hemolysis does occur. The possibility that the peptides induce hemolysis is encompassed, as long as the peptides are more toxic to the pathogenic cells than they are to the blood cells (RBCs). Jacob has undertaken *in vivo* experiments which show that survival of mice is increased when the peptide is administered (together

with tumor cells), relative to survivability when the peptide is withheld. If it were true that the peptides of Jacob were more toxic to RBCs than they are to tumor cells, the physiologist of ordinary skill would have expected a shortening of the survivability (of the mice) following peptide administration, rather than a lengthening. According to one interpretation, Jacob has gone a step further in demonstrating relative toxicity than has been done in the instant specification. The instant specification shows only that the toxicity (of the claimed peptides) to cancer cells is greater in vitro than the toxicity of the peptides to RBCs in vitro. What matters more, when treating a cancer patient, is for the efficacy of the peptides to be greater against tumor cells than RBCs in vivo. Accordingly, the artisan of ordinary skill would have expected that toxicity to tumor cells is greater than toxicity to RBCs when administered to a patient; the claims are thus rendered obvious.

D. Lukton 3/17/04

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

ROBERT A. WAX
PRIMARY EXAMINER